SYSTEMATIC REVIEW

Epidemiology of rheumatoid arthritis, clinical aspects and socio-economic determinants in Pakistani patients: A systematic review and meta-analysis

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Abstract

Objectives: The study aimed to evaluate literature on rheumatoid arthritis disease in Pakistani patients, to have an understanding about its epidemiology, clinical aspects and socio-economic determinants.

Methods: The review study was conducted from December 2017, to May 2018. An online search was conducted in international and local health databases using appropriate search keywords as well as scanning reference lists of related articles. Literature published after year 2000 that reported epidemiological, demographic, clinical and socio-economic data of Pakistani rheumatoid arthritis patients was included. Meta-analysis was performed where possible. This systematic review was registered on the international prospective register of systematic reviews PROSPERO (CRD42018090582).

Results: Of the 334 research articles found, 29 (8.7%) were selected. Patients were mostly females, but no study explored impact of disease on household and family role functioning of rheumatoid arthritis-affected women in Pakistan. Most patients were uneducated (55%) and unemployed; had low disease knowledge (N = 149, 74.5%) and poor adherence to disease-modifying anti-rheumatic drugs (N = 23, 23%). Point prevalence of rheumatoid arthritis reported from Karachi was high at 26.9%. Moderate disease activity, i.e., 4.5±0.7 and mild functional disability (N = 66, 51.6%) were seen in RA patients. Almost half (N = 799, 46.9%) had comorbidities. Almost a fifth proportion of RA patients had dyslipidaemia as a comorbidity (N = 134, 16.77%) and higher cardiovascular risk score as modifiable risk factor. Undiagnosed depression (N = 134, 58.3%) and low bone mineral density (N = 93, 40.6%) were reported in RA patients. Direct monthly treatment cost of disease was significantly high considering patients' socio-economic status, i.e., USD 16.47 – 100.68. Most commonly used drug was methotrexate.

Conclusion: There is a paucity of data on Pakistani rheumatoid arthritis patients' demographic and socio-economic parameters, especially the gender element.

Keywords: Rheumatoid arthritis, Epidemiology, Prevalence, Socio-economic, Patients, Pakistan. (JPMA 69:389; 2019)

Introduction

Rheumatoid arthritis (RA) is a chronic inflammatory disease of joints characterised by pain, stiffness, inflammation and decreased mobility. It results in joint deformity, decrease work ability, productivity and subsequently reduces quality of life of an individual. Studies estimate that 0.5% - 1% of population is affected by RA globally and rank the disease next to osteoarthritis and gout as major causes of disability.[1] Figures for prevalence of RA vary across geographic regions and populations.

Literature reports higher prevalence of RA in polar countries compared to tropical countries.[2] Several studies have estimated RA prevalence rate around the globe. For instance, prevalence in Serbia was 0.35% with female predominance.[2] A figure of 0.31% was reported from France, 0.41% from Italy and 0.55% in Lithuania.[3] In Asian countries, it was 0.26% in South Korea while in Japan it was between 0.6% - 1%.[4] In African countries, a prevalence of 0.13 was reported in Algeria, 0.9 in Congo, 0.2 in Egypt and 0.9 from South Africa. RA prevalence was less than 0.5 in Nigeria.[5] In Canada, the prevalence was 0.9%.[6] In South Asia, the disease prevalence in India was 0.75%.[7] In Pakistan, evidence from the past highlight a prevalence of 0.142% from Karachi with female predominance.[1]

Apart from disease prevalence, literatures also report comorbidity status of RA patients. Depression, metabolic disorders such as diabetes mellitus (DM) and dyslipidaemia as well as hypertension (HTN) were commonly observed comorbidities in this population along with high cardiovascular risk score, altered blood pressure (BP) and glucose levels as modifiable risk factors.[4,8] In addition, direct cost of RA treatment has been reported from developed as well as developing countries. Study in Canada reported an average direct annual cost of

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USD 5,531 for RA treatment per patient.[6] Another study in Turkey reported average annual direct medical cost of € 2,000 to 2,385.[9]

In this context, RA epidemiology in Pakistan along with its socio-economic determinants, clinical aspects and cost of treatment needs to be evaluated to have an insight into disease information and understanding the problems of this population.

The current review study was planned to summarise all existing research literature pertaining to Pakistani RA patients that reported prevalence, associated comorbidities, demographics such as gender, age of disease presentation, education level, etc., and clinical aspects of the disease. Additionally, socio-economic determinants such as residence, income, employment, monthly family income and cost of managing RA in this population stratum were assessed.

Materials and Methods

The review study was conducted from December 2017, to May 2018. The date of last search was May 14, 2018. PubMed, Google Scholar, Pakistan Science Abstracts and PakMediNet, databases were searched using keywords 'rheumatoid arthritis-Pakistan', 'rheumatological disorders-Pakistan', 'arthralgia-Pakistani-patients', socio-economic-status-rheumatoid-arthritis-Pakistan', and 'comorbidities-rheumatoid-arthritis-Pakistan'. Reference list of the selected articles were also scanned. Literature in English language, with an abstract and, highlighting any determinants that contributed to our objectives were included.

The types of articles included were cross-sectional, interventional, parallel group trials and retrospective studies published after the year 2000. Only those studies that reported epidemiological, demographic, clinical and socio-economic data were included. Studies that employed the American College of Rheumatology (ACR) 1987, 2010 ACR/European League Against Rheumatism Collaborative Initiative (EULAR) and physician's assessment based on any of the above-mentioned criteria were included.[10-14] Studies that were conducted in hospital settings with institutional permission or ethical approval were included. Studies that were found to be irrelevant or not fulfilling the above-mentioned criteria were excluded.

Studies conducted in Pakistani RA patients for documenting age of presentation and gender were included. Patients with arthralgia, inflammatory rheumatological disorders and rheumatoid arthritis were included for documenting prevalence of disease.

Information pertaining to patients' demographics such as age of illness presentation, gender, education was sought from the studies. Socio-economic determinants, namely marital status, employment and monthly family income, were also noted. Comorbidity information and cost of treatment were also documented. Meta-analysis was performed where possible. It was done by analysing data from studies measuring similar outcomes using 95% confidence intervals (CI).

Results

Of the total 334 studies, 138(41.3%) came from PubMed, 51(15.2%) from Pakistan Science Abstracts, 41(12.2%)

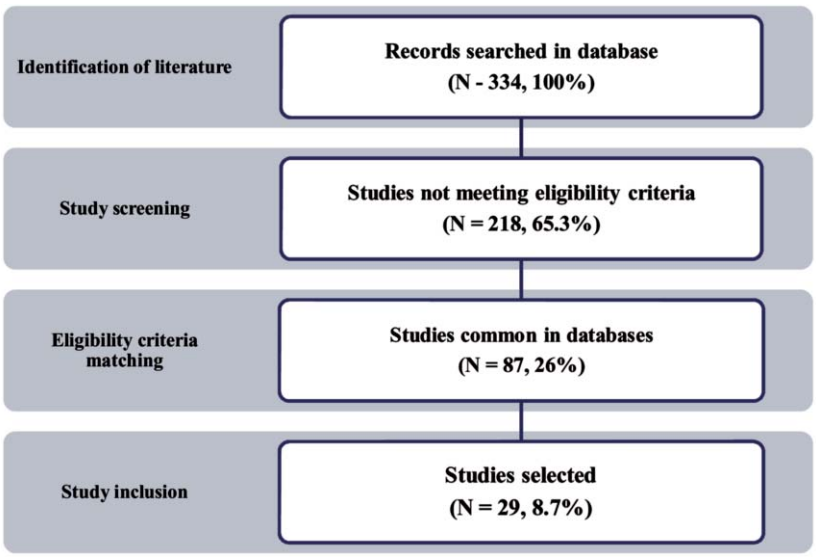

Figure-1: Study selection process.

Table-1: Studies reporting point prevalence (%) of rheumatoid arthritis.

Author/ year	Venue	Year of study	Prevalence (%)
Shamim et al., (2015)[18]	Jinnah Postgraduate Medical Centre	August 2013 - January 2014	26.9%
Rais et al., (2014)[17]	Liaqat National Hospital	September 2006 - September 2012	21.7%
Alam et al., (2011)[16]	Liaqat National Hospital	January 2005 - June 2007	12.9%

Table-2: Studies reporting prevalence, gender distribution and age of presentation among Pakistani rheumatoid arthritis patients.

Author/year	City	Venue	Year	Sample size	Gender distribution (M/F in %)	Age of presentation (years)
Khalil et al., (2017)[15]	Rawalpindi	Fauji Foundation Hospital	January - June 2015	200 patients	6/94	50±12.96
Jalil et al., (2017)[28]	Rawalpindi	Military Hospital, Arthritis Research Centre & Rehmat Noor Clinic	October 2009 - October 2013	500 enrolled patients	26/74	45 - 60
Masood et al., (2017)[27]	Rawalpindi	Fauji Foundation Hospital	May 2015 - December 2015	128 patients	4.7/95.3	51.75±9.25
Wagan et al., (2017)[26]	Lahore	Central Park Medical College Hospital	July 2016 - January 2017	246 enrolled patients	23.6/76.4	Female (48.4±7.6) Male -(50.2±7.5)
Erum et al., (2017)[20]	Karachi	Jinnah Postgraduate Medical Centre	November 2013 - May 2014	200 patients	11.5/88.5	36.31±10.46
Wazir et al., (2016)[30]	Peshawar	Postgraduate Medical Institute, Lady Reading Hospital	October 2014 - October 2015	166 patients	30/70	35±2.12
Zafar et al., (2016)[25]	Lahore	Shaikh Zayed Hospital	July 2014 - June 2015	384 patients	25.3/74.7	43.8±10.6
Wagan et al., (2016)[24]	Lahore	Sheikh Zayed Federal Post Graduate Medical Institute	April 2014 - April 2015	106 patients	18.9/81.1	45.1±9.5
Imran et al., (2015)[23]	Lahore	Fatima Memorial Hospital	March 2014 - May 2014	102 enrolled patients	24.5/75.5	43.5±11.9
Abbasi & Haidri (2014)[21]	Karachi	Indus Hospital	December 2010 - May 2011	120 patients	11.2/88.8	32 - 51
Athar et al., (2014)[34]	Karachi	Ziauddin University Hospital	July 2014 - September 2014	40 patients	22.5/77.5	-
Ishaq et al., (2013)[19]	Karachi	Jinnah Medical College Hospital	July 2011 - December 2011	240 patients	29.2/70.8	Female (53.4±15.6) Male (55±10.7)
Zammurrad et al., (2013)[29]	Islamabad	Pakistan Institute of Medical Sciences (PIMS)	November 2011 - April 2012	138 patients	8/92	42.9±12.0
Ahmad et al., (2011)[22]	Lahore	Fatima Memorial Hospital	August 2006 - December 2006	63 patients	14.3/85.7	46±12.6

Table-3: Studies reporting comorbidities among Pakistani rheumatoid arthritis patients.

Author/year Reference	Comorbidity	Assessment tool
Masood et al., (2017)[27]	Depression (47.7%)	Beck Depression Inventory II[36]
Wagan et al., (2017)[26]	Dyslipidaemia (43.5%) Hypertension (37.4%) Diabetes Mellitus (22.8%)	Patient history and prescribed medications were checked. Lipid lowering medications were checked for diagnosing dyslipidaemia followed by laboratory analysis, mercury sphygmomanometer was used to assess hypertension. Fasting blood sugar and prescription containing hypoglycaemic drugs and insulin was checked to assess diabetes mellitus.
Erum et al., (2017)[20]	Dyslipidaemia (53.5%)	National Education Cholesterol Programme 2004[37]
Zafar et al., (2016)[25]	Metabolic syndrome (31.3%)	National Education Cholesterol Programme 2004[37]
Wagan et al., (2016)[24]	Hypertension HTN (22.6%) Diabetes mellitus DM (17%) Chronic kidney disease CKD (1.9%) Atrial Fibrillation AF (1.9%)	Mercury sphygmomanometer 3x was used to confirm HTN. Patient history, FBS>126 mg/dL, and prescribed drugs were checked as well as use of insulin was also inquired for confirming DM. Electrocardiogram and clinical examination was used along with patient history to confirm the diagnosis of AF. Cockcroft and gault method was employed for CKD staging
Imran et al., (2015)[23]	Depression (71.5%)	Beck Depression Inventory II[36]
Abbasi &Haidri (2014)[21]	Fibromyalgia (25.83%)	ACR 1990[38]
Athar et al., (2014)[34]	Co-morbidities were present in patients (72.5%)	Patient medical records
Zammurrad et al., (2013)[29]	Fibromyalgia (22.4%)	ACR 1990[38]
Ishaq et al., (2013)[19]	Restless leg syndrome (20%)	Allen RP et al. 2003[39]

from PakMediNet and 104(31.3%) from Google Scholar. Leaving out those that did not meet eligibility criteria, i.e., 305(91.3%), the remaining 29(8.7%) were selected for review (Figure-1).

There was a single cross-sectional study, by Khalil et al., that reported demographic and socio-economic information of RA patients in Pakistan. The study was solely based on patients living in urban areas. It reported that slightly more than half of patients (55%) were uneducated while rest were educated at different levels. Furthermore, it also reported monthly family income of patients; the majority (66.5%) had monthly family income between PKR 5,000 and 20,000 while a small segment (13.5%) had an income less than PKR 5,000. A small proportion (11.5%) had income greater than PKR 50,000.[15]

In terms of prevalence, a total of 3 studies were conducted

Table-4: Studies reporting risk factors in patients.

Author/ year	Risk factors	
Wagan et al., (2017)[26]	Body mass index greater than 30 kg/m^2	Male patients 53.4% Female patients 46.8% Cumulative 48.4%
	Framingham risk score (FRS) greater than 11 i.e. moderate	Male patients 20.7% Female patients 19.1%
	Framingham risk score (FRS) greater than 20 i.e. high	Male patients 53.4% Female patients 10.6%
	Moderate to high FRS score	Cumulative 40.2%
	Systolic Blood pressure SBP greater than 120 mm of Hg	Male patients 50%
	Diastolic blood pressure (DBP) greater than 80 mm of Hg	Female patients 33.5% Cumulative 37.4%
	Fasting blood sugar level greater than 126 mg/dL	Male patients 24.1% Female patients 22.3% Cumulative 22.8%
	Serum Low density lipoprotein (LDL) level greater than 160 mg/dL	Cumulative 43.5%
	Smoking	Male patients 55.2% Female patients 3.7% Cumulative 15.9%
Wagan et al., (2016)[24]	Family history of myocardial infarction (35.8%)	
	Framingham risk score (FRS) greater than 20 i.e. high (31.1%)	
Wazir et al., (2016)[30]	Body mass index greater than 27.5 kg/m2(36.14%)	
Athar et al., (2014)[34]	Family history of RA (100%)	

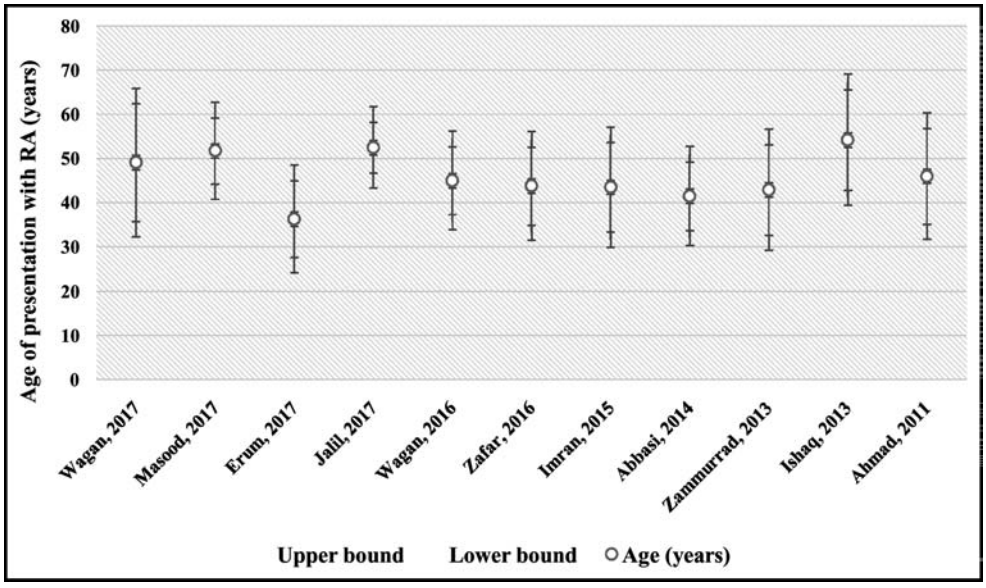

Figure-2: Studies reporting mean age of presentation with rheumatoid arthritis.

in Karachi from years 2011 to 2015. A retrospective study by Alam et al., reported RA prevalence of 12.9%.[16] This was followed by another study employing similar methodology that reported a higher prevalence, i.e., 21.7%.[17] A prospective study by Shammim and colleagues reported a prevalence of 26.9% in patients (Table-1).[18]

Regarding the age of presentation, a total of 13 cross-sectional studies gathered data of 2593 RA patients from 2006 to 2017. The mean age of presentation of rheumatoid arthritis patients was 44 years, 95% CI [44.39 - 44.42] (Table-2; Figure-2).

Studies were also assessed region-wise. In Karachi, the reported mean age was 53.4±15.6 years and 55±10.7 years for female and male RA patients respectively.[19] Erum et al., reported mean age of 35.31±10.46 years.[20] Abbasi and colleagues reported a range for age between 32-51 years for RA patients.[21] Four studies conducted from 2006 to 2017 involved 671 patients overall. Meta-analysis revealed that the mean age of presentation was 46.5 years (95% CI: 46.51 - 46.59).

In Lahore, a mean age of 46±12.6 years was reported by Ahmad et al.[22] Another study in Lahore reported figures for age at 43.5±11.9 years.[23] Two studies in Lahore by Wagan et al., and Zafar et al., reported similar figures, i.e.,

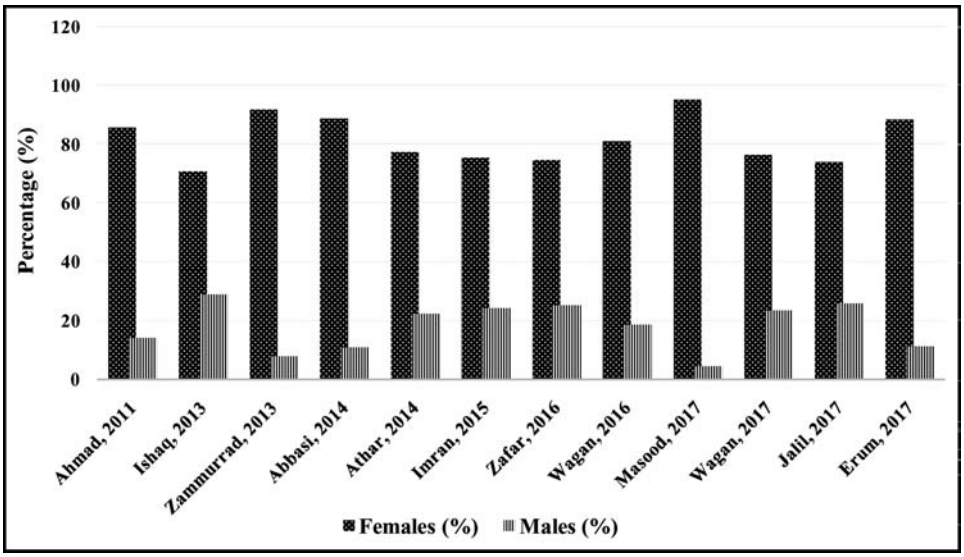

Figure-3: Gender distribution of patients reported by studies.

45.1±9.5 years and 43.8±10.6 years respectively.[24,25] A recent study reported the age of female patients at 48.4±7.6 years and 50.2±7.5 years for male RA patients.[26] To summarize the findings, five studies were carried out between 2011 and 2017 involving 901 patients. Meta-analysis revealed that the mean age of presenting with RA was 46 years (95% CI: 46.13 - 46.19).

In Rawalpindi, two studies by Khalil et al., and Masood et al., reported a mean age of 50±12.96 years and 51.75±9.25 years respectively.[15,27] Study by Jalil and colleagues reported an age range of 45-60 years.[28] Cumulatively, three studies were conducted in 2017 that gathered data from 828 RA patients and reported a mean age of presentation at 51.5 years (95% CI: 51.38-51.44). In Islamabad, a study involving 166 RA patients reported a mean age of 42.9±12 years (95% CI: 42.82-42.98).[29] In Peshawar, a sole study reported a mean age of 35±2.12 years in 138 RA patients (95% CI: 34.92-35.08].[30]

Age at presentation was also assessed for juvenile RA (JRA) patients. A study was conducted from 2002 to 2004 in 91 patients. The mean age of onset was reported at 10.7±4 years.[31] Another study from 2008 to 2011 documented data of 185 JRA patients. The mean age of presentation was 10.45±3.55 years.[32] Another study reported a mean age of 9.94 years in 70 JRA patients.[33] Meta-analysis revealed a mean age of 10.4 years (95% CI: 9.87-10.93] at presentation.

Besides, 14 cross-sectional studies documented gender distribution in a total sample of 2633 RA patients and reported a mean proportion of females that comprised of 81.6% (95% CI: 81.66-81.67) of the total RA patients enrolled (Figure-3). Gender was also assessed in region-wise studies.

In Karachi, a study reported that female patients accounted for 70.8% of total patients enrolled.[19] This was followed by studies of Athar et al., and Abbasi et al., that reported a high female predominance, i.e., 77.5% and 88.8% respectively.[21,34] A recent study reported that 88.5% of RA patients enrolled were females.[20] To summarize the findings, four studies were conducted in Karachi from 2013 to 2017 that gathered data from 600 RA patients and reported a mean proportion of 81.2% (95% CI: 81.21-81.23) for female patients.

In Lahore, Ahmad and colleagues reported that females accounted for 85.7% of all patients enrolled in the study.[22] Another study reported a proportion of female patients to be 75.5%.[23] Studies by Wagan et al., and Zafar et al., in 2016 reported a figure of 81.1% and 74.7% for female patients respectively.[24,25] A recently published study reported figure of 76.4% for females suffering from RA.[26] To sum up, five studies were carried out in Lahore from 2011 to 2017 that involved 901 RA patients and reported that female patients account for 78.7% of the total enrolled patients (95% CI: 78.67%-78.69%).

In Rawalpindi, studies by Khalil et al., and Masood et al., reported a female proportion of 94% and 95.3% respectively.[15,27] Another study by Jalil and colleagues reported a percentage of 74% for female RA patients.[28] Cumulatively, three studies were conducted in Rawalpindi in 2017 that involved 828 patients that reported a mean female proportion of 87.76% (95% CI: 87.75%-87.77%). In Islamabad, a study in 2013 involved 138 RA patients and reported that most (92%) of the patients were females (95% CI: 91.98%-92.02%].[29] In Peshawar, a study in 2016 reported 70% female RA patients.[30]

In terms of JRA, Ahmad and colleagues reported that there were 49(54%) females and 42(46%) males. Another study reported around 50.3% female JRA patients.[32] A study conducted by Naz and colleagues reported 40(57.1%) female and 30(42.9%) male JRA patients.[33]

As for common clinical presentations of RA in patients, a

study in 185 patients reported that 144(78%) had morning stiffness while 126(68%) had fever.[32] In another study comprising 58 adult patients, 28(48.2%) had polyarthralgia, 14(24.1%) had fever and 13(22.4%) had morning stiffness.[34]

A total of 10 cross-sectional studies from 2011 to 2017 documented comorbidities in 1704 patients. Of the total, 799(46.9%) patients had comorbidities. Of them, 214(26.78%) presented with dyslipidaemia, 134(16.77%) with depression, 120(15%) metabolic disorders, 116(14.5%) HTN, 74(9.2%) DM and 62(7.8%) fibromyalgia. Also, 48(6%) patients had restless leg syndrome, 1(0.13%) suffered from chronic kidney disease (CKD) and atrial fibrillation (AF), i.e., 1(0.13%).[19-21,23-27,29,35] A small segment of RA patients was reported to be comorbid without any details of associated illnesses (Table-3).[34] The criteria to evaluate patients for depression was the use of Beck Depression Inventory.[36] For dyslipidaemia and metabolic syndrome, it was the National Education Cholesterol Program.[37] ACR 1990 was used to evaluate fibromyalgia and criterion outlined by Allen and colleagues, was used in evaluating RA patients with restless leg syndrome.[38,39]

There were four cross-sectional studies from 2014 to 2017 that reported modifiable and non-modifiable risk factors for RA and other ailments in patients. It included genetic predisposition, moderate-to-high Framingham risk scores (FRS), body mass index (BMI) greater than 27.5 kg/m^2, smoking (especially in male patients), systolic blood pressure (SBP) greater than 120mm Hg and, diastolic blood pressure (DBP) greater than 80mm Hg, as well as fasting blood glucose (FBS)[24,26,30,35] (Table-4).

A study comprising of 102 RA patients to document depression using Beck Depression Inventory (BDI) scale reported 31(30.4%) patients with mild depression, 23(22.5%) with moderate depression and 19(18.6%) with severe depression.[23] Another study that investigated undiagnosed clinical depression in 128 RA patients reported mild depression in 50(39.1%), moderate depression in 8(6.3%) and severe depression in 3(2.3%) patients.

To summarize these findings, during 2015-17, undiagnosed clinical depression was investigated in a total of 230 patients using BDI scale that found mild depression in 81 (35.2%) patients, moderate depression in 31 (13.5%), while 22 (9.6%) patients had severe depression.[23,27,36]

A study investigated bone mineral density (BMD) using dual energy X-ray absorptiometry (DEXA) scan in 229 RA patients and reported that 93(40.6%) of them had osteoporosis, while 86(37.5%) had osteopenia.[40]

Three studies reported disease activity in RA patients using disease activity score (DAS-28). Abbasi and colleagues reported a mean DAS-28 score of 4.9 (95% CI: 3.66-5.71) in 89 patients and 7.04 (95% CI: 6.62-7.64) in 31 patients having RA and fibromyalgia.[21] Another study reported average DAS-28 score of 4.1±1.2 in RA patients and 5.4±1.5 in patients with RA and fibromyalgia.[29] Imran et al., reported that out of total 102 patients, 33(32.35%) had low disease activity, 34(33.33%) had moderate while 35(34.31%) had high disease activity.[23] The latter did not provide average score. Meta-analysis revealed that former two studies reported an average DAS-28 score of 4.5±0.7, i.e., moderate disease activity in RA patients and 6.22±1.2, i.e., high disease activity in patients with RA and fibromyalgia.

A study conducted in 128 RA patients documented functional disability using Health Assessment Questionnaire (HAQ). It reported disability in 80(62.6%) patients.[41] Of them, 66(51.6%) had mild functional disability, 12(9.4%) had moderate disability and 2(1.6%) had severe functional disability. The functional disability was significantly correlated ($p<0.05$) with depression.[27] Another study reported an average HAQ score of 2.86±4.371 in 102 RA patients.[23]

A study compared the effectiveness of methotrexate (MTX), leflunomide (LEF) and combination therapy with both as well as their safety profile in a randomised clinical trial. It enrolled 73 patients for 6 months. The evaluation criteria were DAS-28 and EULAR response criteria.[12,14] The study reported that MTX and LEF were equally effective, however, combination therapy could not demonstrate any superiority. Common adverse drug reactions (ADRs) reported were increased serum levels of alanine amino transferase (ALT), increased frequency of infections, alopecia and nausea.[42]

Ishaq et al., reported an elevated risk of HTN in 144 RA patients who received LEF over a year and 51(41%) patients were diagnosed with pre-HTN or HTN after a year.[43] A study employed treat-to-target approach using MTX in 50 patients over 6 months and reported remission in 17 (34%) and low disease activity in 29 (58%) patients.[44]

MTX was also the most common disease-modifying anti-rheumatic drug (DMARD) prescribed to 81 (43.8%) JRA patients of total 185 patients.[32] Another 6-month prospective study evaluated efficacy and safety of rituximab (RTX) in patients with active RA who were previously on MTX or LEF and found that RTX was an

effective treatment option in RA patients who had active disease despite using MTX or LEF. However, the study reported anaphylactic reaction, herpes zoster infection and increased upper respiratory tract infections (RTIs) as notable ADRs; myocardial infarction (MI) and hypertensive crisis were major adverse drugs events (ADE) reported during RTX use.[45]

Only a single study reported disease awareness in 200 RA patients and found that 3(1.5%) patients had considerable awareness while 48(25%) were partially aware and 149(74.5%) were not aware of their disease state.[15]

A study reported adherence to MTX in 100 RA patients and highlighted that 23(23%) patients were non-adherent to their regimen. Social factors such as low awareness and family support as well as economical factor, i.e., unaffordability of MTX contributed to non-adherence.[46]

A study conducted in Karachi by Waheed and colleagues in 2006 estimated a monthly cost of RA treatment between USD 16.47-82 in most patients (73.8%) attending the clinic[37]. The current monetary value increases to USD 20.41-100.68 if adjusted for USD value in September 2018.[47] Another study conducted in Chenab Nagar, Pakistan, reported an average annual RA treatment cost of USD 1194 per patient that accounted for 41% of a patient's gross annual income as treatment cost.[48]

Discussion

RA results in debilitating consequences on a patient's life, including physical, psychological, social and economic impact. Only a single study reported residential status of RA patients that was urban. Half of the patients surveyed were uneducated.[15] Employment status of this population stratum has never been reported. Patients had a nominal monthly family income.

The prevalence of RA is steadily increasing in Pakistan. We reviewed three studies from Karachi and observed an increasing RA prevalence. The prevalence was 12.9% in 2011 and 21.7% in 2014. This implied that prevalence of RA hypothetically increased with a factor of 2.2 per year between 2011 and 2014. The latest figure for RA prevalence was 26.9% reported in 2015 that represents a greater than 5% increase in one year. This highlights that prevalence of RA in Pakistan is higher than European and African countries as well as Japan.[2,3,5,49] To calculate population standardised prevalence of RA, population data of Karachi district was sought from Pakistan Bureau of Statistics (PBS).[50] However, due to the non-availability of population data, the population-standardised prevalence could not be calculated.

Furthermore, we observed 13 published studies for the mean age of presenting with RA and reported a figure of 44.4 years. Patients in this age group are usually employed and their work-ability may be impacted by the disease. This has been mentioned as the most expensive adverse outcome of RA followed by its treatment costs.[51-53] Most patients observed were females with a mean proportion of 81.6% which is consistent with findings from studies conducted worldwide where, apart from elderly patients, studies conducted in JRA patients have also reported female predominance.[31-33] Evidence highlights that major segment of RA population around the globe is middle-age females, however, the severity and disease course perceived by majority of clinicians is gender non-specific.[54,55] Women suffering from RA face social consequences of the disease, including inability to carry out daily activities and reduced work-ability.[56] They have greater responsibilities to fulfil, i.e., physical, psychological and emotional needs of the family. However, this aspect has not been given its due attention as highlighted in literature. Household functioning is an important area of productivity that is related to women. During review, it was observed that majority of Pakistani women were associated with household activities. It is important to evaluate their household functioning, family role and productivity as it may have been impacted by the disease.[57]

Comorbidities of Pakistani RA patients were also observed. Most commonly occurring comorbidities observed were dyslipidaemia, depression, metabolic disorders, HTN and DM_{58}. Most common non-modifiable risk factor for RA was positive family history. Other risk factors reported were obesity, moderate-to-high cardiovascular risk scores, altered BP and FBS>126 mg/dL. Smoking was common among male patients. The findings were in concordance with results of a French study conducted in 17 countries that reported similar figures for depression, DM and HTN as associated illness in RA patients.[4] However, figure obtained for dyslipidaemia as an associated illness was higher for Pakistani patients. Similar figures were reported from Moroccan patients.[8] In this context, studies conducted in middle-aged Pakistani population highlight the presence of coronary artery disease (CAD) risk factors namely dyslipidaemia, DM, HTN and obesity, especially in females while smoking is an additional determinant in males.[58] Dyslipidaemia and cardiovascular riska further increase with DM as comorbidity.[59-62] The same can be applied to RA patients. Unhealthy dietary pattern among Pakistani population is reasoned as a contributory factor for this predicament.[63]

We observed that patient knowledge regarding RA was inadequate.[15] There is dearth of literature on knowledge and awareness regarding RA and its treatment among Pakistani patients. Lack of disease awareness and low knowledge has been previously reported by Naqvi and colleagues in Pakistani patients.[64] Awareness is considered a determinant to medication adherence.[65] We observed that a quarter of RA patients were not adherent to their DMARD therapy and one of the reasons reported was low awareness.[46] Studies have called for increasing awareness using patient-centred approach or through counselling by rheumatologists or pharmacists.[66]

Studies report that managing RA results in direct financial burden on patients. Few studies have estimated direct cost of managing communicable diseases such as tuberculosis and poliomyelitis and non-communicable disease such as diabetes mellitus in Pakistan.[67-70] However, there were only two studies that roughly estimated the direct cost of RA management. The mean out-of-pocket expenditures in 2006 ranged from PKR 1,000 to PKR 5,000.[47] However, recent figures are quite high with average annual cost of US$ 1194 per patient. This accounted for almost a fourth of patients' annual income and represented a 14.5% increase in direct cost of RA treatment during 2006-14.[48] This increase in costs was comparatively lower than figures obtained from both developed as well as other developing countries.[6,9,71,72] However, they may be significantly high from a Pakistani patient's perspective considering mean age of illness presentation and work-disability.

MTX demonstrated better safety and efficacy in Pakistani patients and was most common DMARD used for treatment. Several interventional studies ranging from 6 months to 2 years, including clinical trials demonstrated effectiveness of MTX besides its better safety profile and cost-effectiveness.[73] However, adherence to DMARDs could be increased by increasing disease awareness and by providing patient counselling.

RA demographics have not been significantly documented in Pakistani population. Available literature highlights poor education level among RA patients. Hence, the knowledge and awareness regarding disease warrants further investigation. A study did estimate disease awareness in Pakistani patients but did not employ a validated questionnaire.[15] There is a need to report disease knowledge in RA patients using a validated questionnaire. Point prevalence has been reported from urban population of Karachi which could not be standardised due to non-availability of population statistics. Prevalence studies are needed to estimate from other parts of the country incorporating both urban and rural populations. The cost of treatment appears to be quite high considering socio-economic status of this population stratum. Further research is needed in employed patients to estimate disease burden, productivity and income loss due to RA. Pharmacists have the potential to counsel patients and educate them about disease and medication adherence. Further investigation in this area is needed.[74]

Conclusion

Over the last decade, there have been very few studies conducted on RA patients in Pakistan. Patients were mostly females; uneducated and unemployed. Point prevalence of RA reported from Karachi was high. Most common comorbidity observed in Pakistani RA patients was dyslipidaemia. Higher cardiovascular risk score was the most common risk factor. Undiagnosed depression, low BMD, moderate disease activity and mild functional disability were also reported in Pakistani RA patients. RA direct treatment costs were significantly high considering patients' socio-economic status.

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